

## 8

## INTERACTION OF SELECTION, MUTATION, AND DRIFT

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In the previous chapter, we treated selection as an effectively deterministic process, making the assumption that the stochastic force of random genetic drift is negligible relative to the power of selection, while also ignoring the origin of new variation by mutation. Such an approach often works well when the focus is on short-term evolutionary issues. However, with weak selection operating on individual loci over long time scales, selection, mutation, and drift can interact to pattern variation both within and among populations in significant and sometimes counterintuitive ways. As all populations are finite in size, and all genomes are subject to mutation, it is essential that we now turn to these matters. Although most of the material in this chapter is confined to one- and two-locus systems, the resultant principles will provide the basic building blocks for more complex models for the evolution of quantitative traits to be presented in subsequent chapters.

Whereas mutation and drift respectively introduce and remove variation from populations, selection can have either effect, depending on whether it is directional or stabilizing in nature. Of special interest is the degree to which all three forces interact to define the distribution of allele frequencies in an equilibrium population (or more precisely, in a quasi-equilibrium population, as with drift there is always some stochastic wandering of allele frequencies around a long-term expectation). One of the key issues considered in the following pages concerns the amount of variation maintained by the balance between opposing selection and mutation pressures. We initially address this matter by retaining the assumption of an effectively infinite population size. Some simple extensions of this model demonstrate that recurrent deleterious mutation imposes a fitness load on all populations, defined by the mutation rate, but surprisingly independent of the individual mutational effects. We then evaluate the situation in which drift is sufficiently strong to compete with or even overpower the effects of selection. The latter issue is of special interest when we consider selection on a quantitative trait, as strong selection at the phenotypic level does not necessarily translate into strong selection on any particular underlying locus.

Because the ways in which genes evolve often depend on the background context, we also use this chapter to introduce some key issues regarding the evolution of multilocus systems. First, drawing on results outlined in Chapter 3 for the effects of linkage on the effective population size for a chromosomal region, we explore how this translates into a reduction in the efficiency of selection for advantageous alleles. Second, using compensatory mutations as an entrée into the matter of epistasis, we evaluate the extent to which such pairwise changes are promoted in small vs. large populations. Third, as mutation and recombination rates differ substantially among species (Chapter 4), we consider the degree to which selection might be responsible for such variation, i.e., the extent to which the genetic machinery itself is the product of adaptive evolution as opposed to being an inevitable byproduct of cellular constraints.

## SELECTION AND MUTATION AT SINGLE LOCI

Many of the central questions in population and quantitative genetics concern the mechanisms that are responsible for the standing levels of molecular and quantitative variation that are observed in natural populations. Here we introduce a few classical models for the balance between the opposing forces of mutation and directional selection. Our preliminary focus will be on the simple case of two alleles, as this will serve as the foundation for more complex models for the maintenance of quantitative variation covered in later chapters.

Consider a locus with an advantageous allele **A** and a mutant allele **a**, with respective frequencies  $1 - p$  and  $p$ . Let  $u$  be the mutation rate from **A** to **a**, and  $v$  be the rate of back mutation to **A**. We assume random mating, constant viability selection, and an effectively infinite population size. From Chapter 7, following selection, the new frequency of **a** is

$$p' = p \frac{W_a}{\bar{W}} \quad (8.1)$$

where  $W_a$  is the marginal fitness of **a**, and  $\bar{W}$  is the mean population fitness. Letting  $p''$  be the allele frequency following mutation, we have

$$p'' = (1 - v)p' + u(1 - p') = (1 - u - v)p' + u \quad (8.2)$$

This follows because  $1 - v$  is the fraction of **a** that remains unchanged following mutation, while a fraction  $u$  of all **A** alleles (with frequency  $1 - p'$ ) mutate to **a**. Thus, under the joint action of selection and mutation, the new frequency of **a** is

$$p'' = (1 - u - v)p \frac{W_a}{\bar{W}} + u \quad (8.3)$$

Haldane (1927) was the first to consider the stable equilibrium frequencies under this model of opposing mutational and selection pressures. Letting the fitnesses of genotypes **AA**, **Aa**, and **aa** be 1,  $1 - hs$ , and  $1 - s$ , the equilibrium frequencies

$\tilde{p}$  satisfying  $\Delta p = p'' - p = 0$  are given by the solutions of the rather complicated formula

$$(1 - \tilde{p})^3 s(2h - 1) + (1 - \tilde{p})^2 [2 - 3h + uh + v(1 - h)] + (1 - \tilde{p}) [-s(1 - h) + u(1 - hs) + v(1 - 2s + hs)] - v(1 - s) = 0 \quad (8.4)$$

(Bürger 2000). Provided  $0 < s < 1$  and  $h \leq 0.5$ , this expression has a single stable equilibrium, and considerable simplification is possible in a number of biologically realistic cases. For example, for the case of neutrality ( $s = 0$ ), the equilibrium is defined by the opposing forces of mutation

$$\tilde{p} = \frac{u}{u + v} \quad (8.5)$$

The situation of most interest here, where allele **a** is at a selective disadvantage, concerns the polymorphism maintained by a balance between selection and mutation. To simplify the solution, it is generally assumed that back mutation to the advantageous allele is a negligible force. There are two justifications for such an assumption. First, unless the selection coefficient is small relative to the mutation rate, the frequency of the mutant allele will be so low that back-mutation will be a second-order effect. Second, although functional genes may mutate to deleterious alleles by numerous mechanisms, precise back-mutations to normal alleles will necessarily be much rarer events, i.e.,  $v \ll u$ . Letting  $v = 0$ , Equation 8.4 reduces to a more manageable, quadratic equation, with solution

$$\tilde{p} = \frac{\sqrt{[hs(1 + u)]^2 + 4(1 - 2h)us + (1 + u)hs}}{2(2h - 1)s} \quad (8.6a)$$

In the unlikely event that **a** is a dominant deleterious mutation ( $h = 1$ ),

$$\tilde{p} = \frac{u}{s} \quad (8.6b)$$

whereas if **A** is recessive ( $h = 0$ ),

$$\tilde{p} = \sqrt{\frac{u}{s}} \quad (8.6c)$$

in both cases assuming  $s > u$ , and for the general case of intermediate dominance ( $0 < h \leq 0.5$ ),

$$\tilde{p} = \frac{u}{hs}, \quad \text{provided } h \gg \sqrt{u/s} \quad (8.6d)$$

A number of other special cases are presented in Nagylaki (1992) and Bürger (2000).

The multiple-allele version of this model is straight-forward to obtain. Suppose there are  $k$  alleles  $\mathbf{A}_1, \dots, \mathbf{A}_k$  and let  $u_{ij}$  be the probability that an  $\mathbf{A}_i$  allele mutates to an  $\mathbf{A}_j$  allele. Letting  $u_i = \sum_{j \neq i} u_{ij}$  be the total mutation rate from allele  $\mathbf{A}_i$  to any other allele, and assuming constant viability selection followed by mutation and then random mating, the allele-frequency change equations become

$$p'_i = \frac{1}{W} \left( (1 - u_i) W_i p_i + \sum_{j \neq i} u_{ji} W_j p_j \right) \quad (8.7)$$

where  $W_i$  is the marginal fitness of allele  $\mathbf{A}_i$ . The equilibrium behavior of this system can be quite complex, and with sufficiently strong mutation, the possibility of stable cycles exists (Bürger 2000).

Clark (1998) examined a special case of the multiple-allele model in which there is one optimal allele and heterozygotes for single mutations have fitness  $1 - hs$ , while those for two different mutant alleles have fitness  $1 - ks$ , where  $k$  is a measure of complementation between two deleterious alleles (with  $k = 0$  implying that each allele compensates for the other allele's deficiencies). Under this model, multiple deleterious alleles are maintained by mutation pressure, and provided  $k < 1$ , the sum of their frequencies is higher than expected under the two-allele model. This is because interallelic complementation reduces the magnitude of selection operating on mutant alleles jointly present in the same genotype.

**Example 8.1.** How much variation can mutation maintain when the mutant allele is lethal ( $s = 1$ )? From Equation 8.6b, the equilibrium frequency of a dominant lethal allele is

$$\tilde{p} = u$$

whereas

$$\tilde{p} = \sqrt{u}$$

for a recessive lethal (Equation 8.6c). The first expression applies regardless of the population size, and the approximate nature of the second expression can be seen by noting that the rate of loss,  $2p^2$  must equal the rate of gain of mutant alleles,  $2u(1 - p^2)$ .

Because  $u \ll 1$ , these expressions predict that recessive lethals should be much more common than dominant lethals, a pattern that is seen for numerous human genetic disorders (Cavalli-Sforza and Bodmer 1971). Equations 8.6b,c are often used to estimate the lethal mutation rate for various diseases under the assumption that the observed frequencies of lethal alleles are at mutation-selection equilibrium (e.g., Kondrashov 2003).

For a dominant lethal, the frequency of selected individuals in the equilibrium population is

$$\text{freq}(\mathbf{aa}) + \text{freq}(\mathbf{Aa}) = u^2 + 2u(1 - u) \simeq 2u$$

Conversely, for a recessive, the frequency of selected individuals is

$$\text{freq}(\mathbf{aa}) = (\sqrt{u})^2 = u$$

Thus, despite the great disparity in allele frequencies for dominant and recessive lethals, because  $u$  is expected to be very small, there is only a twofold difference in the expected frequencies of affected individuals.

What about the equilibrium mean fitness of the population? For the dominant allele

$$\bar{W} = \text{freq}(\mathbf{AA}) = (1 - u)^2 \simeq 1 - 2u$$

while for the recessive,

$$\bar{W} = 1 - \text{freq}(\mathbf{aa}) = 1 - u$$

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**Example 8.2.** Albinism in humans is caused by a recessive allele, with an estimated frequency of albinos of around  $1/20,000$  (Cavalli-Sforza and Bodmer 1971). If we assume that albinos are at a slight selective disadvantage ( $s = 0.1$ ) and that we are at mutation-selection equilibrium, what is the estimated mutation rate to albino alleles? Assuming Hardy-Weinberg,  $\tilde{p}^2 = 1/20,000$ , and from Equation 8.6c,

$$\tilde{p}^2 = \frac{1}{20,000} = \left( \sqrt{\frac{u}{0.1}} \right)^2$$

which implies  $u = 5 \times 10^{-6}$ . Conversely, if we assume a mutation rate of  $u = 10^{-5}$ , the strength of selection against albinism can be inferred from

$$\tilde{p}^2 = \frac{1}{20,000} = \frac{10^{-5}}{s}$$

implying  $s = 10^{-5} \cdot 20,000 = 0.2$  i.e., an 80% reduction of fitness in albinos.

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## SELECTION AND DRIFT AT SINGLE LOCI

In the preceding section, we assumed a situation in which the forces of selection and mutation are powerful enough to ignore the stochastic consequences of random genetic drift, at least in the short term. This deterministic approach to population genetics yields explicit equilibrium solutions for allele frequencies, usually with no oscillatory behavior. In reality, however, drift plays a significant role in all long-term population-genetic contexts. For example, even when selection against deleterious mutations is strong, the defective alleles segregating in a population today will generally be descendants of entirely different mutations than those millenia in the past. All mutations eventually experience one of two alternative fates, complete loss from the population or fixation at a frequency of 1.0. (Although even in the latter case, the definition of fixation can be a bit fuzzy, in that by the time a mutation reaches fixation, some members of its genealogy may themselves have acquired alternative mutations).

Our focus now becomes the probability of fixation of an allele by the spread of its descendants to a total frequency of 1.0. In general, drift opposes selection in that sampling of gametes to form each consecutive generation results in random deviations in allele frequencies. If drift is strong relative to selection, a favored allele may stochastically decrease in frequency and eventually become lost, while a disadvantageous allele may increase in frequency and sometimes even become fixed. Throughout the following subsections, we ignore the effects of recurrent mutation, focusing instead on the fate of a pre-existing allele or newly arisen mutations.

Most of the theory of the interaction between selection and drift was developed for a single diallelic locus under viability selection, in which case the change per

generation in allele frequency can be thought of as the sum of the changes under selection and under drift,

$$\Delta p = \Delta p_s + \Delta p_d$$

where  $\Delta p_s$  is given by Equation 7.1b, and  $\Delta p_d$  (the per generation change due to drift) is a random variable. Under drift, there is no directional tendency for the change in allele frequency, and hence  $E(\Delta p_d) = 0$ . Thus, the simplest measure of the strength of drift is the expected variance in allele-frequency change due to gamete sampling, which under the standard Wright-Fisher model of genetic drift (Chapter 2) is defined by the binomial distribution,

$$\sigma^2(\Delta p_d) = \frac{p(1-p)}{2N_e} \quad (8.10)$$

where  $p$  is the allele frequency prior to sampling, and  $N_e$  is the variance effective population size (Chapter 3). If  $\sigma^2(\Delta p_d)$  is small relative to  $\Delta p_s$ , allele-frequency changes will not be dramatically different from their expectations under selection in an infinite population, but drift dominates when  $\sigma^2(\Delta p_d)$  is large relative to  $\Delta p_s$ .

Consider the situation in which alleles have additive fitness effects, such that the genotypes **AA**, **Aa**, and **aa** have respective fitnesses 1,  $1+s$ , and  $1+2s$ . Letting  $p$  be the frequency of allele **a**, if selection is weak ( $|s| \ll 1$ ), then from Equation 7.2,  $\Delta p_s \simeq sp(1-p)$ . Comparing this with Equation 8.10, when  $2N_e|s| \gg 1$ ,  $|\Delta p_s| \gg \sigma^2(\Delta p_d)$ , i.e., selection dominates drift. Conversely, drift is expected to dominate selection when  $2N_e|s| \ll 1$ . A useful heuristic is to think of the power of drift scaling as  $1/(2N_e)$ , so that  $2N_e s$  is approximately the ratio of the power of selection to drift.

This argument is not quite precise because the variance of allele-frequency change is only a rough indicator of the sampling properties of the distribution. However, **diffusion theory**, an approach used to approximate the dynamics of certain well-behaved random processes, gives an essentially complete description of the dynamics of a diallelic locus under drift and selection. Appendix 1 provides an introduction to numerous results from diffusion theory, several of which we draw upon throughout this chapter.

### Probability of Fixation Under Additive Selection

There is no possibility of a perfectly stable polymorphism when drift and selection interact. Indeed, even in the case of overdominant selection (where there is a stable equilibrium in an infinite population, Chapter 7), one allele will eventually drift to fixation unless both homozygotes are lethal. Under this view, all new mutations must eventually become either lost or fixed at the population level, and those that become fixed will be subject to replacement by subsequently arising mutations. Thus, when finite populations are considered, we need to think in terms of fixation probabilities and times for the transient persistence of mutations. Even highly favorable alleles have fixation probabilities less than 1.0 to a degree that depends on the initial frequency  $p_0$ , the strength of selection, and the effective population size  $N_e$ .

Denote by  $p_f(p_0)$  the probability that an allele starting at initial frequency  $p_0$  becomes fixed. As noted in Chapter 4, under neutrality, the probability of fixation

depends only on an allele's initial frequency regardless of population size, so that

$$p_f(p_0) = p_0 \quad (8.11)$$

This is not the case for an allele under selection. When allelic effects on fitness behave additively, such that each copy of allele **a** changes fitness by  $s$  (giving fitnesses of 1,  $1 + s$ , and  $1 + 2s$ ),

$$p_f(p_0) \simeq \frac{1 - e^{-4N_e s p_0}}{1 - e^{-4N_e s}} \quad (8.12a)$$

$$\simeq p_0 + 2N_e s p_0 (1 - p_0) \quad \text{when } 2N_e |s| \leq 1 \quad (8.12b)$$

These expressions hold for both beneficial ( $s > 0$ ) and deleterious ( $s < 0$ ) alleles. Equation 8.12a, due to Kimura (1957) with a slightly improved version given by Cash (1977), is derived using diffusion theory in Appendix 1. Equation 8.12b, due to Robertson (1960), relies on the Taylor-series approximation  $e^{-x} \simeq 1 - x + x^2/2$  for  $|x| \ll 1$  to further simplify Kimura's result. While diffusion approximations work well for the fixation probabilities of favorable alleles (Carr and Nassar 1970), they can significantly *overestimate* the fixation probabilities of deleterious alleles, especially when  $N_e s \leq -1$ . Bürger and Ewens (1995) examine the matter in detail, developing upper and lower bounds for the fixation probabilities for strongly deleterious alleles.

It is critical to note that even when an allele is strongly selected, drift plays a powerful role when the allele frequency is near zero or one. Starting with a single copy of an advantageous allele (with frequency  $p_0 = 1/(2N)$ , where  $N$  is the absolute size of the population), Equation 8.12a implies that the probability of fixation is approximately  $2s(N_e/N)$  when  $4N_e s \gg 1$ . As we expect  $N_e$  to generally be  $\ll N$  (Chapter 3), this implies that a newly arisen favorable mutation is usually lost by drift, no matter how beneficial. However, once the frequency of a strongly beneficial allele becomes sufficiently high, fixation is almost certain. For example, if  $N_e s p_0 \geq 0.5$ , the probability of fixation exceeds 0.70, while if  $N_e s p_0 \geq 1$ , the probability of fixation exceeds 0.93. Note also from Equation 8.12b that  $p_f(p_0) \simeq p_0$  if  $4N_e |s| \ll 1$ . Thus, recalling Equation 8.11, even if  $s \neq 0$ , an allele behaves as if it is neutral over all allele frequencies provided the power of drift,  $1/(2N_e)$ , overwhelms the power of selection,  $s$ . To reflect this fact, such alleles are said to be **effectively neutral**.

A number of other useful approximations for alleles with additive effects on fitness have been derived from diffusion theory. For example, Kimura (1969) found that the cumulative contribution of a new mutation to the population-level heterozygosity (summed over all generations until lost or fixed) is equal to

$$H_T = \left( \frac{4N_e}{N} \right) \left( \frac{S - 1 + e^{-S}}{S(1 - e^{-S})} \right) \quad (8.13)$$

where  $S = 4N_e s$ . For neutral mutations ( $S = 0$ ),  $H_T = 2N_e/N$ , which when multiplied by the number of new mutations arising at the locus (or nucleotide site) per generation ( $2Nu$ ) yields  $4N_e u$ , the expected heterozygosity at drift-mutation equilibrium (Chapter 2).

When scaled to the neutral expectations, both the fixation probability and the cumulative heterozygosity become simple functions of  $S$ . Viewed in this way, it can

be seen that although both the relative fixation rate and the heterozygosity increase with  $S$ , the former responds much more sharply (Figure 8.1). This is because deleterious mutations that essentially never fix in a population will nevertheless transiently contribute to the heterozygosity prior to being eliminated by selection, whereas positively selected mutations will be driven through the population relatively rapidly, contributing to heterozygosity for only a relatively short period.

–Insert Figure 8.1 Here–

Further insight into these points can be achieved by considering the mean number of generations to loss and fixation of new mutations, approximations of which have also been obtained via diffusion theory. For example, the mean number of generations until complete loss of a new mutation with deleterious heterozygous effect  $s$  is

$$t_l = 2(N_e/N)[\ln(2N/S) + 0.423] \quad (8.14a)$$

provided  $S \gg 1$  (Kimura and Ohta 1969b; Nei 1971). This may be compared to the conditional time to loss of a neutral mutation,

$$t_l = 2(N_e/N) \ln(2N) \quad (8.14b)$$

(derived in Appendix 1). More general expressions, which require some numerical integration can be found in Kimura and Ohta (1969a). A useful approximation for advantageous mutations with additive effects is that, conditional on fixation, the expected number of generations spent at frequency  $x/(2N)$  is

$$\Phi(x) = \frac{2N_e(1 - e^{-Sx})(1 - e^{-S(1-x)})}{SNx(1-x)(1 - e^{-S})} \quad (8.15)$$

(from Equation 8.66 in Kimura 1983). Summation of Equation 8.15 over  $x = 1$  to  $2N - 1$  yields the mean time to fixation. For a neutral mutation ( $S = 0$ ), this expression reduces to  $\Phi(x) = 2N_e/N$  for all  $x$ , and as there are  $2N$  frequency classes, the total time to fixation becomes  $4N_e$  generations, in accordance with results presented in Chapter 2.

### Probability of Fixation Under Arbitrary Selection

More generally, if the genotypes **aa**, **Aa**, and **AA** have fitnesses 1,  $1 + s(1 + h)$ , and  $1 + 2s$ , diffusion theory (as developed in Appendix 1) gives the fixation probability of allele **A** as

$$p_f(p_0 | s, h) \simeq \frac{\int_0^{p_0} e^{G(x)} dx}{\int_0^1 e^{G(x)} dx} \quad (8.16a)$$

where

$$G(x) = -4N_e s x [1 + h(1 - x)] \quad (8.16b)$$

As mentioned above, the most frequently required fixation probability is that for a new mutant introduced as a single copy,  $p_0 = 1/(2N)$ , which under random mating and at least partial dominance becomes

$$p_f \left( \frac{1}{2N} \right) \simeq \frac{2N_e s(1+h)}{N[1 - e^{-4N_e s(1+h)}]} \quad (8.17a)$$

This shows that the probability of fixation of a new mutation is largely determined by the heterozygous effect, as almost all copies of a mutation remain in this state until the allele frequency has achieved a moderately high level. For a complete recessive ( $h = -1$ ), the approximation leading to Equation 8.17a breaks down, and higher-order terms in the approximation of Equation 8.16a are required. For strong selection on heterozygotes ( $4N_e s(1+h)$ ), a good approximation is given by

$$p_f \left( \frac{1}{2N} \right) \simeq \frac{\sqrt{4N_e s/\pi}}{N} \quad (8.17b)$$

(see Example A1.7 for details).

If there is direct inbreeding due to mating of close relatives (beyond the amount of long-term inbreeding that is naturally generated by drift), Equation 8.16a still holds, but now with

$$G(x) = -4N_e s x \{2f + (1-f)[1 + h(1-x)]\} \quad (8.18a)$$

where  $f$  is a measure of the departure of genotypes from Hardy-Weinberg expectations, defined (in Chapter 2) by the frequency of heterozygotes,  $2p(1-p)(1-f)$  (Caballero and Hill 1992). Using Equation 8.16a, the fixation probability now becomes

$$p_f \left( \frac{1}{2N} \right) \simeq \frac{2N_e s [2f + (1-f)(1+h)]}{N} \quad (8.18b)$$

(Caballero and Hill 1992; Caballero 1996), which for a complete recessive ( $h = -1$ ) reduces to

$$p_f \left( \frac{1}{2N} \right) \simeq \frac{4N_e f s}{N} \quad (8.18c)$$

Thus, with even a small amount of inbreeding, the probability of fixation of a beneficial recessive allele is considerably higher than under random mating (Equation 8.17b) due to the elevated exposure in homozygotes (Caballero et al. 1991). In contrast, inbreeding has much more moderate effects on the fixation probabilities of alleles with additive ( $h = 0$ ) or dominant ( $h = 1$ ) fitness effects.

By causing localized inbreeding, population subdivision can also influence the probability of fixation. Whitlock (2003) found that for a wide variety of population structures, the probability of fixation of a new beneficial mutation is well approximated by  $2N_e s(1+h)(1 - F_{ST})/N$ , where the effective and total population sizes ( $N_e$  and  $N$ ) are defined at the metapopulation level, and  $F_{ST}$  is an index of population subdivision (defined as the fraction of metapopulation variation of neutral allele frequencies that is distributed among populations). Note that with complete population subdivision ( $F_{ST} = 1$ ), fixation is impossible at the metapopulation level, as mutations are confined to the demes in which they arise.

Expressions for effective population sizes under a number of metapopulation structures were presented in Chapter 3, parallel expressions for  $F_{ST}$  can be found in most of the literature cited there. In the case of the ideal island model with symmetric migration between demes and equal contributions of all demes to the entire metapopulation (Chapter 3),  $N_e = N/(1 - F_{ST})$ , and the preceding expression reduces to  $2(1+h)s$ , showing that in this particular case the probability of fixation is independent of the magnitude of population subdivision and simply equal to twice the selective advantage in heterozygotes (Maruyama 1970). Analyses of much more complex population structures (Slatkin 1981; Barton 1993) are all special cases of Whitlock's (2003) expression, provided the assumption of equal deme productivity is met, and the modifications necessary when this condition are violated are developed in Whitlock (2003) as well. The more complex situation in which the strength of selection varies among demes has been taken up by Whitlock and Gomulkiewicz (2005).

Otto and Whitlock (1997) provide results for fixation probabilities in populations of changing size, showing that selection is more effective in growing populations (increasing the probabilities that favorable alleles are fixed and deleterious alleles are lost) than in declining populations. This result has obvious implications for managed populations. Fortunately, the limiting expression for the fixation probability of alleles with additive effects (given above as  $2sN_e/N$ ) applies to populations that are changing in size, provided appropriate modifications are made in the definition of  $N_e$  (Otto and Whitlock 1997). A number of additional diffusion results are given for a diallelic locus in Appendix 1, but unfortunately, diffusion results for multiple alleles are generally unavailable.

### Expected Allele Frequency in a Particular Generation

A number of applications arise in quantitative genetics where it is useful to know the expected allele frequency at time  $t$ ,  $E(p_t)$ , particularly in attempts to predict the response to selection. While exact results can be obtained from probability transition matrices (Carr and Nassar 1970; Hill 1969a) and good approximations can be derived from diffusion theory (Appendix 1; Maruyama 1977; Ewens 2004) and other approaches (Curnow and Baker 1968, 1969; Pike 1969), these methods tend to be numerically intensive. Fortunately, simple approximations have been developed for weak selection.

In a finite population, drift can reduce the selection response by progressively diminishing the expected heterozygosity each generation. If we assume weak selection (in the limit, the infinitesimal model discussed in Chapter XX), such that additional changes in allele frequencies associated with selection are relatively minor, from Equation 7.1b, the expected frequency change for an allele under additive selection can be described as

$$E(\Delta p_t) \simeq sE[p_t(1 - p_t)] \simeq sp_0(1 - p_0) \left(1 - \frac{1}{2N_e}\right)^t \quad (8.19)$$

where  $p_0$  is the initial allele frequency. The last approximation follows directly from the expression for the expected heterozygosity for a neutral locus in a finite population in generation  $t$  with a starting allele frequency of  $p_0$ , Equation 2.5. Summing

over generations, the expected frequency after  $t$  generations is

$$\begin{aligned} E(p_t) &= p_0 + \sum_{j=0}^t E(\Delta p_j) \simeq p_0 + sp_0(1-p_0) \sum_{j=0}^t \left(1 - \frac{1}{2N_e}\right)^j \\ &\simeq p_0 + 2N_e s \left(1 - e^{-t/2N_e}\right) p_0(1-p_0) \end{aligned} \quad (8.20a)$$

where the last step follows from the useful approximation

$$\sum_{j=0}^t \left(1 - \frac{1}{2N_e}\right)^j \simeq 2N_e \left(1 - e^{-t/2N_e}\right) \quad (8.20b)$$

More generally, if the genotypes **aa**, **Aa**, and **AA** have fitnesses 1,  $1 + s(1 + h)$ , and  $1 + 2s$ , then for small  $N_e|s|$  and  $N_e|sh|$ , the expected frequency of **A** is

$$E(p_t) \simeq p_0 + 2N_e s p_0(1-p_0) \left[ \left(1 - e^{-t/2N_e}\right) + \frac{h(1-2p_0)}{3} \left(1 - e^{-3t/2N_e}\right) \right] \quad (8.21)$$

These approximations provide a remarkably simple route to obtaining fixation probabilities under weak selection ( $N_e s \ll 1$ ). Because an allele is ultimately either fixed ( $p_\infty = 1$ ) or lost ( $p_\infty = 0$ ), the asymptotic mean frequency as  $t \rightarrow \infty$  is equal to the fixation probability,

$$E(p_\infty) = 1 \cdot p_f(p_0) + 0 \cdot [1 - p_f(p_0)] = p_f(p_0)$$

Thus, taking the limit of Equation 8.18 as  $t \rightarrow \infty$  gives a general expression for the probability of fixation under weak selection and arbitrary dominance,

$$f(p_0) \simeq p_0 + 2N_e s p_0(1-p_0) \left(1 + \frac{h(1-2p_0)}{3}\right) \quad (8.22)$$

For additive fitness effects ( $h = 0$ ), this expression is identical to Equation 8.12b. Equation 8.20a was first derived by Robertson (1960), and Hill (1969a,b) found that this approximation is reasonable provided  $N_e|s| < 1$ . The more general versions (Equations 8.21 and 8.22) were produced by Silvela (1980).

### Fixation of Overdominant and Underdominant Alleles

A case of some interest is the effect of drift on a locus experiencing selective overdominance, where the heterozygote has higher fitness than either homozygote. In an infinite population, such balancing selection permanently maintains both alleles (Example 5.4), whereas drift will ultimately fix one of the alleles in a finite population provided the homozygote is nonlethal. Generally, balancing selection will magnify the time to loss of a polymorphism if the equilibrium allele frequencies under pure selection (i.e., in an effectively infinite population) are intermediate. However, contrary to intuitive expectations, selection in a finite population sometimes *decreases* the expected time to fixation at an overdominant locus (Robertson 1962; Ewens and Thomson 1970; Chen et al. 2008).

If the expected equilibrium frequency is extreme (roughly  $\tilde{p} < 0.2$  or  $\tilde{p} > 0.8$ ), a polymorphism starting at  $\tilde{p}$  is usually lost *faster* under balancing selection plus drift than under drift alone, thereby accelerating the removal of heterozygosity. Such behavior makes sense if we consider that selection keeps allele frequencies fairly close to their equilibrium values. If such values are extreme (near 0.0 or 1.0), the minor allele will be largely confined to low frequencies by selection and impeded from occasionally drifting to a more protective state of moderate frequencies, thereby increasing the likelihood of its loss by drift.

Nei and Roychoudhury (1973) evaluated this issue with respect to newly arisen overdominant alleles with initial frequency  $1/(2N)$ . In this case, the new allele is initially confined to the heterozygous state, so its early fate is largely independent of its own homozygous effect, but largely dependent on the magnitude of its selective advantage over the resident homozygote. Fixation probabilities can only be obtained by numerical analysis in this case, but the results depend only on two parameters,  $N_e(s_1 + s_2)$  and the equilibrium frequency (for an infinite population size)  $\tilde{p} = s_2/(s_1 + s_2)$ , where  $s_1$  and  $s_2$  are respectively the selection coefficients against the homozygotes associated with the mutant and resident alleles. If  $\tilde{p}$  for the allele under consideration is much less than 0.5, the fixation probability is less than the neutral expectation for the reasons noted above. However, if  $\tilde{p}$  is larger than 0.5 (the fitness of the resident homozygote is lower than that of the mutant allele), the fixation probability is always greater than the neutral expectation, even though fixation results in the loss of the optimal (heterozygous) genotype. Moreover, the fixation probability of the mutant allele is only slightly smaller than that predicted by Equation 8.12a when  $s_2$  is used as a selection coefficient (Nei and Roychoudhury 1973). Again, it can be seen that if the ratio of the power of selection to drift  $N_e(s_1 + s_2) \ll 1$ , the system will behave in an effectively neutral fashion.

The mean fixation times for overdominant mutations parallel the patterns of loss of variation that Robertson (1962) noted (Nei and Roychoudhury 1973). When the equilibrium frequency is outside of the range of (0.2, 0.8), the fixation time is lower than the neutral expectation of  $4N_e$  generations, whereas in the interior the rate is elevated, with more extreme behaviors seen at high  $N_e(s_1 + s_2)$  (Figure 8.2). Particularly intriguing is the fact that the fixation time of an overdominant mutation is symmetrical around  $p = 0.5$ , i.e., for a given strength of selection  $N_e(s_1 + s_2)$ , the time to fixation is the same at equilibrium frequencies  $\tilde{p}$  and  $1 - \tilde{p}$ . This means that when the allele is associated with the least fit homozygous type, for the rare occasions in which fixation occurs, it does so just as rapidly on average as when it is associated with the most fit homozygote (and therefore fixes more frequently). Such behavior seems to be related to a remarkable result obtained by Maruyama and Kimura (1974) for mutations with additive effects on fitness – the mean time to fixation of a beneficial mutation, conditional on the mutation actually going to fixation, is identical to the time to fixation of a deleterious allele with the same selection coefficient (but of opposite sign). If a deleterious allele is to become fixed, it must do so as a consequence of some fortuitously rapid and extreme sampling errors. These results clearly demonstrate that balanced polymorphisms with expected frequencies outside of the (0.2, 0.8) range are unlikely to be maintained in natural populations. Further considerations for the situation in which populations are subdivided are

given in Nishino and Tajima (2005).

–Insert Figure 8.2 Here–

Important situations also exist in which a new mutation is underdominant with respect to the resident allele, i.e., has reduced fitness when in the heterozygous state, but equal or higher fitness as a homozygote. In an infinite population, such an allele would always be driven from the population if its marginal fitness at low frequency is less than that of the resident allele. In a finite population, however, there is some chance that the mutant allele might drift to high frequency, transiently taking the population through a reduction in mean fitness, but possibly eventually becoming fixed.

Such a scenario has generated considerable interest in the area of speciation biology, as the fixation of an underdominant mutation in a subpopulation would lead to a situation in which the hybrids resulting from backcrosses to the parental population have reduced fitness, i.e., to at least the first stages of reproductive isolation. Not surprisingly, fixation of an underdominant mutation is only likely to occur if  $N_e$  is sufficiently small for drift to overwhelm the power of selection against heterozygotes.

For the situation in which the two homozygotes have equal fitness and heterozygotes experience a reduction in fitness  $s$ , Lande (1979) found that if  $sN_e/N \ll 1$  (a condition likely to be met based on our previous considerations of empirical information on  $N_e/N$ )

$$f_p(1/2N) \simeq \frac{e^{-N_e s} \sqrt{N_e s / \pi}}{\text{Nerf}(\sqrt{N_e s})} \quad (8.23)$$

where the error function

$$\text{erf}(x) = (2/\sqrt{\pi}) \int_0^x e^{-y^2} dy \quad (8.24)$$

is the cumulative frequency of a unit normal, which can be calculated by various numerical approximations (Abramowitz and Stegun 1972). If the efficiency of selection is sufficiently low ( $N_e s \ll 2$ ),  $f_p(1/2N) \simeq 1/(2N)$ , as expected for an effectively neutral allele. However, if the efficiency of selection is high ( $N_e s > 2$ ),  $\text{erf}(\sqrt{N_e s}) \simeq 1$ , and

$$f_p(1/2N) \simeq (1/N) e^{-N_e s} \sqrt{N_e s / \pi} \quad (8.25)$$

In the context of the study of speciation, the most common sources of interest in the fixation of underdominant mutations are chromosomal rearrangements that cause substantial problems during meiosis in chromosomal heterozygotes, with  $s$  as large as 0.5 being quite plausible (Lande 1979, 1984). Thus, it is of interest that with  $N_e s = 2, 5,$  and  $10$ , Equation 8.25 predicts fixation rates that are 0.22, 0.017, and 0.00016 of the neutral expectation. Such results imply that if heterozygote fitness is greatly reduced, a transition to an alternative allelic state (with equivalent homozygous fitness) is only possible if  $N_e$  is very small. Furthermore, when such fixations do occur, they proceed much more rapidly than the neutral expectation of  $4N_e$  generations (Lande 1979).

Walsh (1982) generalized the above results to the situation in which the fitness in the novel homozygote is elevated to  $1+t$ , such that after passage through a fitness bottleneck, fixation of the underdominant allele will lead to an increase in fitness relative to the ancestral state of the population. Letting  $\theta = N_e s$  and  $\phi = 1 + (t/2s)$ ,

$$f_p(1/2N) = \frac{(2/N)e^{-\theta/\phi}\sqrt{\theta\phi/\pi}}{\operatorname{erf}\{\sqrt{2\theta\phi}[1 - 1/(2\phi)]\} + \operatorname{erf}(\sqrt{\theta/phi})} \quad (8.26)$$

For  $t < 2s$ , the fixation probability is close to that predicted by Equation 8.23, whereas for large  $t$ ,  $f_p(1/2N)$  can moderately exceed the neutral expectation provided  $N_e s$  is not so strong that the allele is incapable of drifting to a high enough frequency to be favored by selection. Thus, we still see that even if the derived allele is highly advantageous in the homozygous state, it is unlikely to fix if the heterozygote fitness is low unless  $N_e$  is quite small. Lande (1979, 1985) shows that such selective valleys are much more likely to be vaulted in subdivided populations, where local extinction and recolonization permit individual demes to make a transition to an alternative genotypic state and then export such a fixed change to a newly opened habitat.

–Insert Figure 8.3 Here–

### Divergence Under Uniform Selection

Although it is generally thought that selection will increase the determinism of a system, this turns out not to necessarily be the case. Cohan (1984) showed that when selection is weak to moderate, starting with identical allele frequencies the probability of divergence between replicate populations can *increase* relative to the situation under pure drift if the frequency of the advantageous allele is sufficiently small. This point can easily be seen as follows. Supposing two replicate populations are segregating alleles **A** and **a** at a locus with  $p = \operatorname{freq}(A) = 0.25$ , then Equation 8.11 implies that under pure drift, the probability that one replicate becomes fixed for **A** and the other for **a** is  $2 \cdot 0.25 \cdot (1 - 0.25) = 0.375$ . Now suppose that **A** is favored by selection, with  $N_e s = 0.5$ . Again assuming  $p_0 = 0.25$ , Equation 8.12a gives the fixation probability of **A** as 0.46, implying that the probability of fixing alternate alleles is  $2 \cdot 0.46 \cdot 0.54 = 0.496$ . Thus, in this case, divergence is substantially *increased* by the interaction between selection and drift. We refer to such behavior as the **Cohan effect**.

In general, the probability of fixing alternate alleles in two replicates is  $2f_p(p) [1 - f_p(p)]$ . Under pure drift,  $f(p) = p$ , giving  $2p(1 - p)$ , which is maximized when  $p = 1/2$ . Thus, the probability of divergence is increased by selection if  $f_p(p)$  is closer to  $1/2$  than  $p$ , and because  $f(p) > p$  for a selectively-favored allele, a requirement for increased divergence under pan-selection is that the starting frequency of the advantageous allele be  $< 1/2$ . The probability of divergence under drift plus selection equals that under drift only when the initial frequency satisfies  $\hat{p} = 1 - f_p(\hat{p})$ . If the initial frequency  $p$  is below  $\hat{p}$ , selection interacting with drift increases the amount

of divergence relative to pure drift. Figure 8.4 shows that the conditions for this to occur are not very restrictive under additive selection.

This observation has a number of practical implications. For example, in Chapter 6 it was noted that a reduced level of population subdivision for a quantitative trait relative to the neutral expectation is often taken to imply the operation of similar selective regimes across subpopulations. But here we see that under identical selection pressures, populations that initiate with low-frequency, advantageous alleles will exhibit levels of divergence more conventionally interpreted as being associated with diversifying selection. Whether allele frequencies, selection coefficients, and drift intensities commonly have the right mixes for uniform selection to enhance the magnitude of phenotypic divergence remains to be seen, but a wide range of conditions appear to yield divergence levels that would be difficult to discriminate from the neutral expectation (Lynch 1986).

–Insert Figure 8.4 Here–

### Selection on Quantitative-Trait Loci

A unique aspect of alleles underlying a quantitative trait is their conditional fitness effects, a phenomenon that is most striking when a trait is under stabilizing selection for an intermediate optimum. If, for example, the mean phenotype is below the optimum, then an allele that contributes positively to the trait will be promoted by selection (provided it does not substantially overshoot the optimum), whereas that same allele would be disadvantageous in a population in which the mean phenotype exceeded the optimum. For the situation in which the mean phenotype coincides perfectly with the optimum, all mutant alleles causing a deviation from the optimum would be selectively disadvantageous. None of these conditions require epistatic effects of the genes on the trait under selection, although because of the nonlinear relationship between phenotype and fitness, there are clear epistatic effects on fitness.

Thus, a key question is the degree to which alleles influencing quantitative variation are subject to fixation, and the extent to which this depends on the allelic effect and the relative contributions of directional and stabilizing selection. For the situation in which selection is purely directional in nature, so that an extreme genotype in one direction is always advantageous, the fixation probability for an advantageous allele at a quantitative-trait locus (QTL) can be obtained by using results from Chapter 7, where the selection coefficient is defined in terms of the additive effect of an allele on the trait and the standardized selection intensity on the trait (the within-generation change in the mean phenotype in units of phenotypic standard deviations). Using such expressions, the expected dynamics of allele frequencies and the probabilities of fixation can be determined by using the expressions developed above, e.g., Equations 8.12a and 8.20a, an approach that will be used extensively in some later chapters.

Here we focus instead on the less straight-forward situation in which the trait is experiencing stabilizing selection. Consider a locus with a pair of additively acting

alleles **a** and **A** segregating at frequencies  $1 - p$  and  $p$ , with the contributions to the phenotype being  $-a$ ,  $0$ , and  $a$  in units of phenotypic standard deviations for genotypes **aa**, **Aa**, and **AA**. Assuming a Gaussian fitness function of the form  $w(z) = e^{-kz^2}$ , where  $z$  is the phenotypic value and the optimum is scaled to equal zero, and using the methods introduced in Chapter 7 to calculate the mean fitness of **A**-bearing individuals and that for the entire population, the selection coefficient is found to be

$$s = -\mu_z \lambda a + \lambda(\lambda \mu_z^2 - 1)(0.5 - p)a^2 \quad (8.27a)$$

where  $\mu_z$  is the mean phenotype, and  $\lambda = 2k/(1 + 2k)$  (Bulmer 1972; Kimura 1981). This shows that the selection coefficient depends not only on the mean phenotype, but also on the allele's additive effect, squared effect, and frequency.

Note that if the population mean is at the optimum ( $\mu_z = 0$ ), Equation 8.27a reduces to

$$s = -\lambda(0.5 - p)a^2 \quad (8.27b)$$

showing that  $p = 0.5$  is an unstable equilibrium, a point made earlier by Robertson (1956). If  $p > 0.5$ , the **A** allele is positively selected, whereas the **a** allele is favored if  $p < 0.5$ . Either way, selection serves to eliminate heterozygosity. Moreover, because the change in frequency of an allele with additive effects on fitness is simply  $sp(1 - p)$ , it can be seen from Equation 8.27b that when the mean is at the optimum, all new mutations are deleterious because  $p = 1/(2N) < 0.5$ .

Using diffusion theory, Kimura (1981) found that the probability of fixation of a new mutation under this model is approximately

$$p_f(1/2N) = \frac{1}{2N \int_0^1 e^{4N_e[\beta_1 x + \beta_2 x(1-x)]} dx} \quad (8.28)$$

where  $\beta_1 = \mu_z \lambda a$ , and  $\beta_2 = 0.5\lambda(1 - \lambda \mu_z^2)a^2$ . This formula, which has to be solved numerically, predicts much higher rates of fixation of mutant alleles than in the case of unconditionally deleterious alleles with the same  $s$  (Kimura 1981). Foley (1987) considered the special situation in which the phenotypic mean coincides with the optimum, with mutations having effects normally distributed around a mean of zero, and found that the average fixation probability of a new mutation can then be approximated by

$$p_f(1/2N) = \frac{1}{2N\sqrt{1 + 2N_e\bar{s}}} \quad (8.29)$$

where from Equation 8.27b,  $\bar{s} \simeq \lambda a^2/2$  is now the average selection coefficient *against* a new mutation with  $p = 1/(2N) \simeq 0$ . Thus, under the assumption of normally distributed mutational effects with quite strong selection, say  $2N_e\bar{s} = 8$ , the average fixation probability of newly arisen mutations would still be  $\sim 33\%$  of the neutral expectation.

It should be noted that these analyses assume that the mean phenotype remains stable regardless of the changes at the locus under consideration. Such a condition would require any change at the focal locus to be fully compensated by alterations at the other loci influencing the trait. This situation is unlikely to ever be strictly true. Computer simulations that allow all loci to freely respond to selection toward a stable optimum suggest that Kimura's results are quite accurate for  $4N_e s < 1$ ,

but otherwise can overestimate the probability of fixation by several fold (Hastings 1987). Hastings (1987) also suggested that when  $N_e s$  is large under this model, on the rare occasions on which fixations occur, they usually do so in pairs that fortuitously compensate for each others' effects, i.e., one increasing and the other decreasing the mean phenotype.

## JOINT INTERACTION OF SELECTION, DRIFT, AND MUTATION

When selection, drift, and mutation operate simultaneously, the allele frequencies in a population of constant size eventually reach a stochastic equilibrium (or stationary distribution),  $\phi(x)$  where  $x$  denotes the allele frequency. Recall from Chapter 2 that we can interpret such an equilibrium in two different ways. First, if we have a large number of replicate populations,  $\phi(x)$  closely approximates the frequency histogram of the numbers of populations with specific allele frequencies at the locus. Conversely, if we follow a population over time and construct a histogram of the historical record of allele frequencies at the locus over a very large number of time points, we would again recover  $\phi(x)$ .

Again, diffusion theory provides a general solution to this problem (Appendix 1). For the simple biallelic case in which mutations from allele **A** to **a** occur at rate  $u$ , and  $v$  is the reciprocal rate, Wright (1949) found that the equilibrium distribution for the advantageous **A** allele is given by

$$\phi(x) = C \bar{W}^{2N_e} x^{4N_e v - 1} (1 - x)^{4N_e u - 1} \quad \text{for } 0 < x < 1 \quad (8.30a)$$

where  $C$  is a constant such that Equation 8.23a integrates to one and hence is a proper probability density (Example A1.3 provides a derivation of this expression).

This fairly general expression can be applied to numerous problems. Consider, for example, the case of a deleterious recessive allele maintained by mutation (with  $u$  being the mutation rate to deleterious alleles, and  $s$  being the selective disadvantage of mutant homozygotes). Letting  $x$  be the frequency of the deleterious allele, the mean population fitness is  $\bar{W} = 1 - sx^2$ , which because  $(1 - y)^{N_e} \simeq e^{-yN_e}$ , yields  $\bar{W}^{2N_e} \simeq e^{-2N_e s x^2}$ . Ignoring back mutation to the advantageous allele, the equilibrium distribution is

$$\phi(x) = C e^{-2N_e s x^2} x^{4N_e u - 1} (1 - x)^{-1} \quad \text{for } 0 < x < 1 \quad (8.30b)$$

a result originally due to Wright (1938).

Nei (1969) provides a broad overview of the dynamics of the allele-frequency spectrum for lethal mutations, including those that are entirely recessive or over-dominant. As neither of these conditions are commonly observed (Lynch and Walsh 1995), we note only some of the results for partially recessive lethals. In this case, the average expected frequency at selection-mutation balance is as given by Equation 8.6d, essentially independent of population size, and provided  $2N_e h s \gg 1$  (i.e., the power of selection against heterozygotes exceeds the power of drift), the variance in allele-frequency is approximately

$$\sigma^2(p) = \tilde{p}/(4N_e h s) \quad (8.31)$$

Nei (1971) and Li (1975) give expressions for the expected numbers of individuals affected by a newly arisen deleterious mutation prior to its elimination by selection.

An area of special interest is the behavior of the four possible nucleotides at a particular site. Denoting the four frequencies as  $x_i$  (where  $i = 1, \dots, 4$ ) and their selection coefficients as  $s_i$  (here assumed to be weak and additive), under the assumption that all nucleotides mutate to each other type at the same rate  $u$ , Equation 8.30a generalizes to

$$\phi(x_1, x_2, x_3, x_4) = C\bar{W}^{2N_e} (x_1x_2x_3x_4)^{4N_eu-1} \quad (8.32)$$

where  $\bar{W} = 1 + 2\sum_{i=1}^4 x_i s_i$  is the mean population fitness. Not surprisingly, the solution to this trivariate ( $x_4$  being defined as  $1 - x_1 - x_2 - x_3$ ) expression is quite cumbersome (Li 1987; Zeng et al. 1989; Bulmer 1991).

Consider, however, the situation in which there is one optimal nucleotide, whose frequency we denote by  $x$ , with the three others having an equal selective disadvantage  $s$  in the heterozygous state. Scaling the fitness of the less-fit alleles to be 1, the mean population fitness is then  $\bar{W} = 1 + 2xs$ , which is closely approximated by  $e^{2xs}$  under the assumption of small  $s$ . The expected frequency of the optimal nucleotide then becomes

$$\tilde{p} = \frac{e^S}{e^S + (u/v)} \quad (8.33)$$

(Li 1987; Bulmer 1991; McVean and Charlesworth 2000). From Equation 8.12a,  $e^S$  is the ratio of fixation probabilities for beneficial and deleterious mutations, and  $u/v$  is the ratio of mutation rates from and to the beneficial allele. As  $N_e \rightarrow 0$ , the expected frequency of the **A** allele approaches the expectation under pure mutation pressure,  $v/(u+v)$ , whereas as  $N_e \rightarrow \infty$ ,  $\tilde{p} \rightarrow 1$ . For low mutation rates (as expected for nucleotide sites), the population will generally be fixed for one or the other allelic types, with  $\tilde{p}$  being the probability that the population is monomorphic for beneficial allele. On the other hand, at very high  $N_e$ , Equation 8.33 expresses the expected frequencies of segregating alleles ( $\tilde{p}$  for the beneficial allele, and  $(1 - \tilde{p})/3$  for each of the three nonoptimal alleles, which are here assumed to be selectively equivalent and equally mutationally interchangeable). In principle, an expression for the expected heterozygosity can then be obtained by jointly accounting for the expected frequencies of the alternative fixed states, the probabilities of fixations between alternative pairs of states (Equation 8.12a), and the total heterozygosity produced during such transitions (Equation 8.13) (McVean and Charlesworth 2000).

## HALDANE'S PRINCIPLE AND THE MUTATION LOAD

Having established the expected allele frequencies at a locus jointly influenced by mutation, selection, and drift, we now consider the price that all organisms pay for the privilege of evolving. Because most mutations are deleterious, and many unconditionally so, for every beneficial allele created by mutation, many more detrimental mutations will be introduced to a population. In populations of sufficiently large size, the majority of such mutations will be kept at low frequency and eventually purged, but the relentless flux of new mutations will nevertheless result in an equilibrium load on the mean fitness in the population (Muller 1950; Crow 1993). Remarkably,

under reasonably general conditions, this load is often essentially independent of the effects of individual mutations.

In an elegant display of population-genetic theory, Haldane (1937) proposed that the reduction in fitness resulting from recurrent deleterious mutations is a function of the mutation rate alone, an observation that has come to be known as **Haldane's principle**. Consider a deleterious recessive allele **a** with selective disadvantage  $s$  in homozygotes. Recalling Equation 8.6d, the mean population fitness associated with this locus is

$$\bar{W} = 1 - s \cdot \text{freq}(\mathbf{aa}) = 1 - s \left( \sqrt{\frac{u}{s}} \right)^2 = 1 - u \quad (8.38a)$$

This shows that because the expected frequency of recessive homozygotes is inversely proportional to their selective disadvantage, the reduction in mean fitness (the **mutation load**) is independent of the strength of selection and simply equal to the deleterious mutation rate per allele. For a deleterious dominant allele with equilibrium frequency  $u/s$ ,

$$\begin{aligned} \bar{W} &= 1 - s [\text{freq}(\mathbf{aa}) + \text{freq}(\mathbf{Aa})] \\ &= 1 - s \cdot \left[ \left( \frac{u}{s} \right)^2 + 2 \left( \frac{u}{s} \right) \left( 1 - \frac{u}{s} \right) \right] \\ &= 1 - 2u + \frac{u^2}{s} \end{aligned} \quad (8.38b)$$

Assuming  $s > u$ , the term  $u^2/s$  is negligible, and the mean fitness is again essentially independent of the strength of selection and simply a function of the mutation rate (in this case, the per-locus rate  $2u$ ). Finally, consider an allele with partial dominance, so that the heterozygote fitness is  $1 - hs$ . Recalling from Equation 8.6d that the equilibrium allele frequency is  $\tilde{p} = u/(hs)$ , the mean population fitness is

$$\begin{aligned} \bar{W} &= 1 - 2hs\tilde{p}(1 - \tilde{p}) - s\tilde{p}^2 \\ &\simeq 1 - 2hs\tilde{p} = 1 - 2hs \left( \frac{u}{hs} \right) = 1 - 2u \end{aligned} \quad (8.38c)$$

so that the expected mean fitness is independent of both  $h$  and  $s$ . Bürger (2000) explores these expressions in considerable detail, confirming that the error in ignoring selection effects in the preceding expressions is of order  $u^2/s$  or smaller. With multiple deleterious alleles per locus, these same expressions apply if  $u$  is interpreted as the total mutation rate of the most beneficial allele to all classes of deficient alleles (Crow and Kimura 1964; Clark 1998).

One key assumption underlying the preceding derivations is that the population is effectively infinite in size. If, on the other hand,  $N_e$  is sufficiently small that the power of drift exceeds that of selection, then we can no longer expect a permanent equilibrium allele frequency at a locus, and can anticipate instead a continual flux of deleterious mutations to the state of fixation. If unopposed for a sufficiently long time, such a condition would eventually reduce mean population fitness to the point at which the average individual would be incapable of replacing itself, leading to population extinction via a **mutational meltdown** (Lynch et al. 1995a,b).

Kimura et al. (1963) first noted that  $N_e$  must be several fold greater than  $1/(hs)$  for Haldane's principle to be closely approximated, further suggesting that the mutational load due to segregating mutations will monotonically increase with decreasing

$N_e$ . However, their study invoked a relatively high level of back mutation in order to maintain a quasi-equilibrium allele frequency. If instead, one treats back mutation as negligible force (for reasons stated above), it can be shown that the load associated with segregating mutations is nonmonotonic with respect to  $N_e$ . The load reaches a maximum (in excess of the Haldane expectation) at the point where  $1/(2N_e) \simeq hs$ , as it is at this point that mutations have a maximum deleterious effect that is still consistent with being highly vulnerable to random genetic drift (Lynch et al. 1995a,b). As  $N_e$  declines below this point, the segregational load approaches zero simply because drift is so strong that few segregating polymorphisms of any kind are maintained, and at this point permanent damage simply accrues via the fixation of deleterious alleles.

A second point to consider is that Haldane's principle assumes a situation in which there are negligible epistatic effects on fitness. Kimura and Maruyama (1966) examined this issue by considering a quadratic fitness function of the form  $w_i = 1 - h_1i - h_2i^2$ , where  $i$  is the number of mutations carried by the individual. With  $h_2 = 0$ , we closely approximate the model of additive effects assumed above, and Haldane's principle continues to hold, with mean fitness being approximately equal to  $e^{-U}$ , where  $U$  is the deleterious mutation rate per diploid genome. However, at the opposite extreme with  $h_1 = 0$ , fitness declines with the square of the number of mutations, and mean fitness is elevated to  $\sim e^{-U/2}$  regardless of the magnitude of  $h_2$ . A more general expression that allows for nonzero values of both  $h_1$  and  $h_2$ , provided by Kimura and Maruyama (1966), demonstrates that this type of **synergistic epistasis** will always reduce the mutational load on a sexual population. In contrast, with **diminishing-returns epistasis**, where the decline in fitness with increasing numbers of deleterious mutations becomes progressively shallower, the mutation load is elevated beyond the Haldane expectation.

Fitness functions involving epistasis have played a significant role in our attempt to understand the evolution of sexual reproduction, primarily because the behavior just noted does not extend to asexual genomes, as first shown by Kimura and Maruyama (1966) in a remarkably simple way. Consider an asexual population of mixed clones, with  $p_0$  and  $p'_0$  being the frequencies of the clone with minimal number of mutations in one generation and the next. Then, accounting for selection and mutation,

$$p'_0 = \frac{p_0 W_0 e^{-U}}{\bar{W}} \quad (8.39)$$

where  $W_0 = 1$  is the fitness of the optimal genotype, and  $e^{-U}$  is the fraction of the members of this class that do not acquire mutations. Note that no assumptions have been made here with respect to the mode of gene action or of the form of the phenotype distribution, and yet at equilibrium ( $p'_0 = p_0$ ) we obtain the very general result that mean fitness  $\bar{W} = e^{-U}$ . Thus, if synergistic epistasis among deleterious mutations is important, a matter on which there is little empirical consensus (Rice et al. 2002; Barton and Otto 2005), a sexual population will have a long-term advantage in terms of mean fitness. Substantial additional work exists on this subject (e.g., Kondrashov 1984, 1988; Charlesworth 1990; Agrawal and Chasnov 2001; Otto 2003; Haag and Roze 2007), but we will now move on to additional matters, as most of our remaining attention is focused on sexual populations.

## FIXATION ISSUES INVOLVING TWO LOCI

There are a number of contexts in which fixation probabilities of alleles are influenced by factors operating at other loci. For example, as discussed in Chapter 3, selection operating on any locus, either positive or negative, results in a reduction in the effective population size in the local chromosomal region, thereby reducing the efficiency of selection operating on all loci linked to the target of selection. Such effects will reduce the fixation probabilities for beneficial alleles, while enhancing the likelihood of fixation of deleterious alleles. In addition, for mutations with contextual (epistatic) effects, fixation probabilities will depend critically on the genetic background, and hence on the frequencies of alternative alleles at interacting loci. All of these factors depend very much on the effective population size, which defines the baseline level of variation expected in a population.

### The Hill-Robertson Effect

We first consider the matter of selective interference created by linked variation involving beneficial alleles. Suppose that the gamete with the highest fitness, **AB**, is initially absent and can only be generated by recombination in **Ab/aB** double heterozygotes. Letting  $x_2$  and  $x_3$  denote the frequencies of the **Ab** and **aB** gametes, if the recombination frequency between the two loci is  $c$ , then the probability of **AB** being generated in the population is equal to the product of the expected frequency of **Ab/aB** heterozygotes and the probability that a random gamete from such individuals is **AB**,  $(2x_2x_3)(c/2)$ . Because  $x_2x_3 \leq 1/4$  and a population with stable size must produce  $2N$  successful gametes, the upper bound to the expected number of **AB** gametes generated in any generation is then  $(2N)(c/4)$ . Thus, if  $Nc < 2$ , fewer than one **AB** gametes will be produced each generation by recombination, so unless there is a strong advantage to **AB**, one of the intermediate gamete types will most likely become fixed before **AB** can reach an appreciable enough frequency to be deterministically promoted by selection. Such fixation of one of the intermediate types will then preclude the generation of **AB** by recombination, leaving new mutation as the only mechanism for such production. For this special case where the optimal gamete is initially absent, Latter (1966b) developed approximate expressions for the mean time to the first appearance of the **AB** gamete by recombination and for its subsequent fixation probability.

Although there is no general expression for the probability of fixation when alleles at two or more loci are competing for fixation, a number of results were developed in the important paper of Hill and Robertson (1966). They were able to obtain a weak-selection approximation for the probability of fixation for the following case. Let two diallelic loci (with designated alleles **A/a** and **B/b**) have recombination frequency  $c$ ,  $p_0$  be the initial frequency of **A**, and  $D_0$  be the initial gametic-phase disequilibrium (as defined in Chapter 2). Assuming completely additive selection (no dominance or epistasis), where each copy of **A** adds  $s_1$  and each copy of **B** adds  $s_2$  to total fitness, the probability that **A** becomes fixed is

$$f(p_0) \simeq p_0 + 2N_e s_1 p_0 (1 - p_0) + \frac{2N_e s_2}{2N_e c + 1} D_0 \quad (8.40)$$

provided that  $2N_e|s_1|$  and  $2N_e|s_2| < 1$ . Comparing this two-locus approximation to the single-locus result (Equation 8.12b) shows that the probability of fixation can be increased or decreased depending on the sign of the initial gametic-phase disequilibrium,  $D_0$ .

When selection is strong ( $N_e|s_1|$  and/or  $N_e|s_2| \gg 1$ ), things get rather interesting. In this case, Hill and Robertson (1966) found by computer simulation that linkage (i.e.,  $c < 0.5$ ) generally *decreases* the probability of fixation of an advantageous allele relative to the single-locus result. If **A** and **B** are favored alleles, linkage has little effect on the probability of fixation of the **ab** gamete, but the probabilities of fixation of the **Ab** and **aB** gametes increase at the expense of the optimal **AB** gamete (Latter 1965; Hill and Robertson 1966). This decrease is maximized when  $N_e c$  is small and both loci have the same effect (e.g.,  $s_1 = s_2$ ), as then there is no selective distinction between the two intermediate gametes, rendering them neutral with respect to each other. This is a significant point, as most theoretical investigations on the effects of linkage on the selection response have assumed loci with equal effects (e.g., Fraser 1957; Latter 1965, 1966a,b; Gill 1965a,b,c; Qureshi and Kempthorne 1968; Qureshi 1968; Qureshi et al. 1968), thereby inflating the importance of linkage.

This general phenomenon of selective interference between linked loci, first noticed by Hill and Robertson, was subsequently nicknamed the **Hill-Robertson effect** by Felsenstein (1974). As discussed in Chapter 3, the primary implication of the Hill-Robertson effect is that selection renders the behavior of linked loci closer to that expected under neutrality by reducing the effective population size for the chromosomal region (Birky and Walsh 1988; Charlesworth 1994; Peck 1994). This effect applies to the efficiency of selection on all non-neutral alleles, both advantageous and deleterious. For example, sometimes a moderately beneficial mutation will arise in tight linkage to a highly detrimental allele at another locus, resulting in very rapid elimination from the population if the net fitness of the chromosomal region is still lower than that of the population mean. In addition, the average substitution rate at a locus generating deleterious alleles is *increased* if that locus is linked to another locus generating either deleterious or beneficial alleles (Birky and Walsh 1988). In other words, the net effect of linkage is to reduce the overall efficiency of selection for fitness-enhancing mutations, magnifying the accumulation of mildly deleterious mutations at the expense of fixing more advantageous alleles.

This realization that the broad spectrum of Hill-Robertson effects is equivalent to a reduction in  $N_e$  greatly facilitates the estimation of fixation probabilities of new mutations subject to background selection and occasional selective sweeps. Indeed, in most contexts that have been examined so far, the standard fixation expressions given above still apply provided the appropriate modifications are made to the definition of  $N_e$  (Stephan et al. 1999), as has also been found for subdivided and growing/declining populations. These redefinitions, which have already been outlined at the end of Chapter 3, again point to the great technical utility of the concept of effective population size.

## Compensatory Mutations

To this point, we have generally been assuming that the magnitude of selection op-

erating directly on an allele is independent of the genetic background (other than effects associated with linkage disequilibrium) on which it resides. However, there are numerous biological conditions in which this will not be the case. Most notable among these is the broad category of compensatory mutation, wherein specific single mutations at either of two loci cause a reduction in fitness, while their joint appearance restores fitness or even elevates it beyond the ancestral state. Such epistatic interactions play a prominent role in Wright's (1931, 1932) **shifting balance theory** for adaptive evolution, under which an adaptive valley is transversed by random genetic drift in a small population, with the locally fixed advantageous genotype then being exported to surrounding demes by migration. At the intramolecular level, compensatory mutations appear to be important in a variety of changes in protein sequences and in the composition of nucleotides in the stems of RNA molecules (Stephan and Kirby 1993; Kondrashov et al. 2002; Kulanthinal et al. 2004; Azevedo et al. 2006).

Ascertaining the conditions under which evolution by compensatory mutation is most likely to occur is challenging because unlike the situation with a single mutation whose fixation depends only on its own initial frequency, the success of a mutation involved in an interlocus interaction depends on the frequency of alleles preexisting at the interacting locus, as well as on the fitnesses associated with the nine possible two-locus genotypes, and on the recombination rate between the two loci. Consequently, no general theory for the long-term evolution of interacting loci has yet been developed, although considerable progress has been made in a number of special cases.

We start by considering the situation in which two loci are fixed for alleles **A** and **B** respectively, inquiring as to the time to reach an alternative state of fixation at both loci, with respective alleles **a** and **b**. We will assume equivalent mutation rates ( $u$ ) from **A** to **a** and **B** to **b**, and initially ignore back mutation. With unidirectional mutation pressure, fixation must eventually occur unless the non-**AB** gametes are lethal.

The simplest scenario in this case, first explored by Kimura (1985), assumes gamete-level selection, such that gametes **Ab** and **aB** have equivalent fitness  $1 - s$  and gametes **AB** and **ab** have equivalent fitnesses of 1.0. At the limit of very small  $N_e$ , such that mutations are limiting and the efficiency of selection is weak ( $4N_e u \ll 1$  and  $4N_e s \ll 1$ ), the degree of linkage can be ignored (as only one locus is polymorphic at a time), and the mean time to fixation of the novel **ab** type is the sum of the waiting times for the two mutational steps,

$$\bar{T} \simeq \frac{1}{2Nu} \left( \frac{1}{2p_{f,d}} + \frac{1}{p_{f,b}} \right) \quad (8.41)$$

where  $p_{f,d}$  and  $p_{f,b}$  are, respectively, the probabilities of fixation of deleterious and beneficial alleles (obtained by applying selection coefficients  $-s$  and  $s$  to Equation 8.12a). Transitions to state **Ab** or **aB** occur at rate  $(2Nu)(2p_{f,d})$ , the product of the population mutation rate and twice the rate of first-step fixation, and then conditional on the first change, the second occurs at rate  $2Nup_{f,b}$ . This expression ignores the additional time to fix mutations, which should be relatively minor under the assumed conditions (Carter and Wagner 2002).

If, on the other hand, selection is much stronger than drift ( $4N_e s \gg 1$ ), so that fixation of the intermediate state is unlikely, then the most likely scenario for

a transition to the **ab** type is that the population initially resides in a state of selection-mutation balance at both loci. Assuming complete linkage, and a selection coefficient  $s$  associated with the **a** and **b** alleles when not combined, the **Ab** and **aB** gametes, each with initial frequency  $u/s$  (from Equation 8.6d), would then serve as staging grounds for mutations to the **ab** type. Mutant **ab** gametes arise at rate  $u$  from each of the intermediate types, and fix in an essentially neutral fashion (as most resident gametes are of type **AB**, with equivalent fitness). Thus, the rate of fixation of the **ab** type is  $(u/s)(2u)$ . Ignoring the time to reach the initial equilibrium and the fixation time for the second mutation ( $\sim 4N_e$  generations), the mean time to fixation is the reciprocal of the rate,

$$\bar{T} \simeq \frac{s}{2u^2} \quad (8.42)$$

(Gillespie 1984; Stephan 1996).

When the **AB** and **ab** states have equivalent fitness, and mutations are reversible, the question then arises as to the long-term rate at lineages switch from one state to the other. Adhering to the reasoning that **Ab** and **aB** gametes will generally be maintained at low levels by selection-mutation balance, and assuming equal back and forward mutation rates, Higgs (1998) elegantly showed that the analysis can be reduced to a one-dimensional diffusion process. The stationary distribution for the frequency ( $x_0$ ) of the **AB** gamete is

$$\phi(x_0) = \frac{1}{(1-z)^{2\alpha-1}} \frac{\Gamma(2\alpha)}{\Gamma(\alpha)^2} [x_0(1-z-x_0)]^{\alpha-1} \quad (8.43)$$

where  $\alpha = 4Nu^2/s$  is the population rate of mutational production of **ab** gametes,  $z = 2u/s$  is the summed frequency of the **Ab** and **aB** gametes, and  $\Gamma$  denotes the gamma function. The frequency of the **ab** gamete is simply  $1-x_0-z$ . With  $\alpha < 1$ , the distribution of  $x_0$  is highly U-shaped, with the probabilities of the population being fixed for alternative **AB** and **ab** states being nearly equal. Higgs (1998) further showed that the average number of generations between peak shifts is

$$\bar{T} = \frac{2\sqrt{N\pi}}{(1-z)\phi[(1-z)/2]} \quad (8.44)$$

Solution of this equation shows that the mean time between compensatory transitions between selectively equivalent endpoints declines with the square root of population size, as larger populations present more targets for compensatory mutations (Figure 8.5). A more general analysis, which allows for weaker efficiency of selection ( $4N_e s < 1$ ), and differential selection and mutation operating on the intermediate states is presented by Innan and Stephan (2001).

–Insert Figure 8.5 Here–

Although the results given above strictly pertain to completely linked sites, Higgs (1998) provides more general expressions, allowing for arbitrary levels of recombination. As a number of other theoretical investigations have demonstrated,

strong linkage substantially accelerates the rate of peak shifts because the frequencies of the low-fitness intermediates remain nearly unchanged during transitions to alternative high-fitness states, ensuring that the population does not pass through a phase of reduced mean fitness (Kimura 1985; Michalakis and Slatkin 1996; Stephan 1996; Innan and Stephan 2001). In contrast, recombination between **AB** and **ab** gametes during a peak shift produces low-fitness intermediates, imposing a bottleneck on mean population fitness, thereby inhibiting the movement from one state to the other.

These kinds of observations, in which a two-locus system, stochastically shifts from one semi-stable state to another through evolutionary time, appear to be closely related (albeit not transparently) to the features of a number of models of complex traits. For example, diallelic models of quantitative traits under stabilizing selection often exhibit multiple equilibria for allele frequencies (including alternative situations of monomorphism and polymorphism), depending on the effects of alternative alleles and the ways of assembling a multilocus phenotype that most closely resembles the optimum (Bulmer 1972; Barton 1986, 1989; Bürger 1989; Gavrillets and Hastings 1994). One can easily imagine that finite populations would wander from one local equilibrium to another through time depending on the history of mutation and drift, although no formal theory on the rate of such internal shifts has been worked out.

Less consideration has been given to the situation in which the **ab** gamete is superior in fitness to the **AB** gamete, but letting the selective disadvantage of the intermediate types with respect to **AB** be  $s_1$ , and the selective advantage of **ab** over **AB** be  $s_2$ , the time to transition from **AB** to **ab** can be obtained by modifying Equation 8.42 to allow for a probability of fixation at the second step of  $2s_2$  (instead of  $1/(2N)$ ), which yields a much lower time to transition than in the case of neutral end points,

$$\bar{T} \simeq \frac{s_1}{4Nu^2s_2} \quad (8.45)$$

Although this expression assumes efficient selection ( $4N_e s_2 \gg 1$ ) in the second step, a more general solution is to use Equation 8.12a in place of  $2s_2$ , which yields Equation 8.42 as  $N_e s_2 \rightarrow 0$ , and also covers situations in which the fitness of **ab** is less than **AB**. As pointed out by Carter and Wagner (2002), this model predicts a substantial elevation in the rate of transition to the **ab** type in large populations, although it also follows that the reverse transition will take place at a diminishingly small rate.

## EVOLUTION OF THE GENETIC MACHINERY

In Chapter 4, we summarized information on phylogenetic variation in mutation and recombination rates. Drawing from the theoretical results outlined above, we now consider the potential evolutionary explanations for the observed quantitative levels of these rates. Like any phenotypic trait, rates of mutation and recombination must be under selection via the effects they impose on individual fitness, but are such rates typically held at optimum intermediate levels by stabilizing selection, or are they pushed to their physiological limits or simply defined by constrained cellular processes?

### Evolutionary Modification of the Mutation Rate

Mutation rates are generally elevated in multicellular species on a per-cell division basis and dramatically so on a per-generation basis. Although the latter is probably due in part to the larger number of germline cell divisions in multicellular species, the evidence also suggests that the DNA replication and repair machinery in such species is somewhat functionally compromised relative to that in unicellular species. This raises the question as to whether elevated mutation rates might be selectively promoted in multicellular species for their long-term effects despite the fact that most mutations are deleterious. However, a central difficulty with this argument is that high mutation rates are much more likely to evolve in predominantly asexual populations (the situation in many unicellular species, but not multicellular taxa), as an absence of recombination is essential if novel mutator alleles are to be pulled to fixation via linkage to the beneficial mutations that they induce (Johnson 1999a; Sniegowski et al. 2000; Wilke et al. 2001; André et al. 2006; Denamur and Matic 2006). For sexual populations, it has proven quite difficult to avoid the conclusion that mutation rates are predominantly driven downwardly by transient linkage of mutator alleles to their recurrent deleterious side effects (Sturtevant 1937; Leigh 1970, 1973; Johnson 1999b).

To see why this is so, note that any allele that magnifies the mutation rate (hereafter, designated as a mutator allele) will necessarily generate statistical associations with defective germline mutations that it induces at linked and unlinked loci. The duration of such disequilibria will depend on the rate of recombination between the mutator and affected loci, but because of the recurrent nature of mutation, new associations will arise each generation, leading eventually to an equilibrium background mutation load. Consider a locus relevant to fitness recombining at rate  $c$  with respect to the mutator locus. If, in the heterozygous state, the mutator induces mutations at the fitness locus at an elevated rate  $\Delta u$  per gene with a reduction in fitness equal to  $hs$  per induced mutation, the selective disadvantage of the mutator allele induced by linkage disequilibrium with this particular fitness locus is

$$s_d \simeq \frac{hs \cdot \Delta u}{1 - (1 - hs)(1 - c)}, \quad (8.46a)$$

assuming  $\Delta u \ll hs$  (Kimura 1967; Dawson 1999), which for unlinked loci reduces to

$$s_d \simeq \frac{2hs \cdot \Delta u}{1 + hs}. \quad (8.46b)$$

Assuming  $L$  chromosomes, each one Morgan in length (a situation closely approximated in most species; Chapter 4), and a haploid genome-wide increase in the deleterious mutation rate of  $\Delta U$ , after accounting for the full distribution of locations of randomly induced mutations, the total induced selection coefficient against the mutator allele is found to be

$$s_{d,T} \simeq \frac{2hs \cdot \Delta U(L - 1 + \phi)}{L(1 + hs)}. \quad (8.47a)$$

where

$$\phi = 1 + \ln \left( \frac{1 + hs - (1 - hs)e^{-1}}{2hs} \right), \quad (8.47b)$$

the approximate elevation in the average induced fitness effect of mutations on the mutator-bearing chromosome relative to that on the other  $L - 1$  unlinked chromosomes (Lynch 2008). For  $0.001 < hs < 0.1$ , which fully covers the range of average mutational effects found in empirical studies (Lynch and Walsh 1998),  $\phi$  is in the range of two to seven.

This relationship shows that the selective disadvantage of a mutator allele is close to twice the product of the heterozygous fitness effect of new mutations ( $hs$ ) and the haploid genome-wide increase in the deleterious mutation rate ( $\Delta U$ ) unless the chromosome number is very small, and even then not likely to be much more than a few-fold higher. The factor by which  $s_{d,T}$  exceeds  $hs \cdot \Delta U / (1 + hs)$  is equivalent to the average number of generations that an induced deleterious mutation remains associated with the mutator responsible for its origin (as can be seen from Equation 8.46b, this factor is two for unlinked loci).

Given the small values for  $hs$  for newly arising mutations and the fact that single amino-acid substitutions in DNA-processing proteins may have arbitrarily small effects on the mutation rate,  $s_{d,T}$  for many mutator alleles may be sufficiently small (relative to the power of genetic drift) to render them effectively immune to the eyes of natural selection. Thus, it is plausible that the elevation of mutation rates in multicellular lineages is not an inevitable consequence of an inherent physiological limitation in such species, but simply an indirect consequence of relatively small effective population sizes (Chapter 4). Given the very low levels of existing mutation rates, there is little room for incremental improvement (the maximum possible reduction being the mutation rate itself), so unless  $2N_e s_{d,T} > 1$ , selection would be unable to promote an *antimutator* allele.

### Selection for Recombination-rate Modifiers

Although we have seen above that for specific positive interactions between two loci (compensatory mutations) a low rate of recombination can facilitate adaptive progress, the fact that restricted recombination almost always induces a more general decline in the efficiency of natural selection via Hill-Robertson effects raises the question as to whether selection can promote the evolution of modifiers that increase the recombination rate. Consider a pair of loci, each of which is segregating for a beneficial and detrimental allele. As noted above, if the beneficial alleles experience coupling disequilibrium, their mutually reinforced fitness will lead to relatively rapid joint fixation of this gametic type, thereby eliminating the disequilibrium. On the other hand, a chance appearance of repulsion disequilibrium will have a prolonged history, as such a condition renders the fitness of the alternative gametic states (e.g., **Ab** and **aB**) more similar to each other. Thus, because natural selection will generally encourage the buildup of repulsion disequilibria, any recombination-rate modifier allele that encourages the breakup of such associations would have an elevated likelihood of being driven to fixation if it were linked with the beneficial chromosomal association that it created. The same argument can be made for recombination-rate modifiers that result in the mutual purging of multiple deleterious mutations. In both cases, recombination magnifies the pool of expressed variation for fitness, thereby enhancing the efficiency of natural selection.

As these types of phenomena bear importantly on the fundamental question of why meiotic sexual reproduction evolved, a substantial body of theoretical work has been devoted to the topic. Because it involves (minimally) three-locus dynamics in finite populations, most population-genetic theory on the evolution of recombination-rate modifiers is highly technical, and with no simple analytical solutions relies heavily on computer simulations. Nevertheless, a few general observations can be made by focusing on the two primary conditions that lead to repulsion disequilibria between beneficial alleles.

First, in the absence of recombination, synergistic epistasis (with fitness declining at an increasing rate with increasing numbers of deleterious alleles) tends to encourage the maintenance of intermediate phenotypes, thereby providing a selective advantage for recombinational production of the double mutants and their more efficient elimination by selection (Eshel and Feldman 1970; Kondrashov 1988; Charlesworth 1990; Barton 1995). Diminishing-returns epistasis has the opposite effect. These general arguments are related to the observation, noted above, that synergistic epistasis results in an elevation in mean population fitness while having no effect in asexual populations. As this effect applies even in the case of populations that are effectively infinite in size, it has been interpreted as an attractive candidate for explanations for the phylogenetic ubiquity of recombination. However, there are numerous arguments as to why epistasis is unlikely to be the primary explanation for the evolution of recombination: as noted above, the evidence on the relative incidence of these two forms of epistasis is mixed at best; the selective effects of synergistic epistasis are greatly diminished when the single-locus effects of mutations are unequal (an issue ignored in most theory, but certainly the case in reality; Butcher 1995); and the number of alternative hypotheses for the evolution of sexual reproduction is quite large (Kondrashov 1993).

This general uncertainty about the ubiquity of synergistic epistasis as a selective agent brings us to the second mechanism that promotes repulsion disequilibrium between beneficial alleles at linked loci – the Hill-Robertson effect, which as discussed above, operates even in the absence of nonadditive gene action. Linkage disequilibria resulting from Hill-Robertson effects are expected to increase with  $N_e$  because larger populations harbor larger numbers of cosegregating loci, so to a degree that increases with population size at least to moderate  $N_e$ , this effect can also promote the evolution of modifiers that magnify the recombination rate. Plausible arguments have been made that the power of this general mechanism for the advancement of recombination-rate modifiers may substantially outweigh that resulting from epistasis, even when synergistic effects are common (Felsenstein and Yokoyama 1976; Otto and Barton 2001; Pálsson 2002; Barton and Otto 2005; Keightley and Otto 2006; Roze and Barton 2006).

What remains unclear is the extent to which modifiers of the recombination rate ever arise with substantial enough effects on the recombination rate (and with sufficiently small negative pleiotropic effects on other aspects of cell biology) to be promoted by these kinds of associative effects. Most attempts to study the matter theoretically have focused on rather extreme situations in which either selection coefficients are very large or the magnitude of the modifier's effect on the recombination rate is extreme, and some approximations suggest that even under these conditions the selective advantage of the modifier can be quite small (Barton and

Otto 2005), perhaps too small to overcome the likelihood of being lost by drift in most cases.

Some empirical observations suggest that strong directional selection in artificial selection programs can lead to the evolution of higher recombination rates (Barton and Otto 2005). However, the review in Chapter 4 (in particular, the data in Figure 4.3) suggests that almost all of the interspecific variation in the genome-wide amount of recombination per physical distance (across eukaryotes) is a simple function of the total number of chromosomes and average chromosome length (and explainable by a simple model that assumes just one to two crossovers per chromosome), leaving very little residual variation in the existing data to be assigned to mechanisms of adaptive fine-tuning. Thus, although models for the evolution of recombination may provide an explanation for the adaptive origin and maintenance of meiotic recombination, it remains to be demonstrated why  $\sim 1$  Morgan/chromosome is an approximate universal across eukaryotes.

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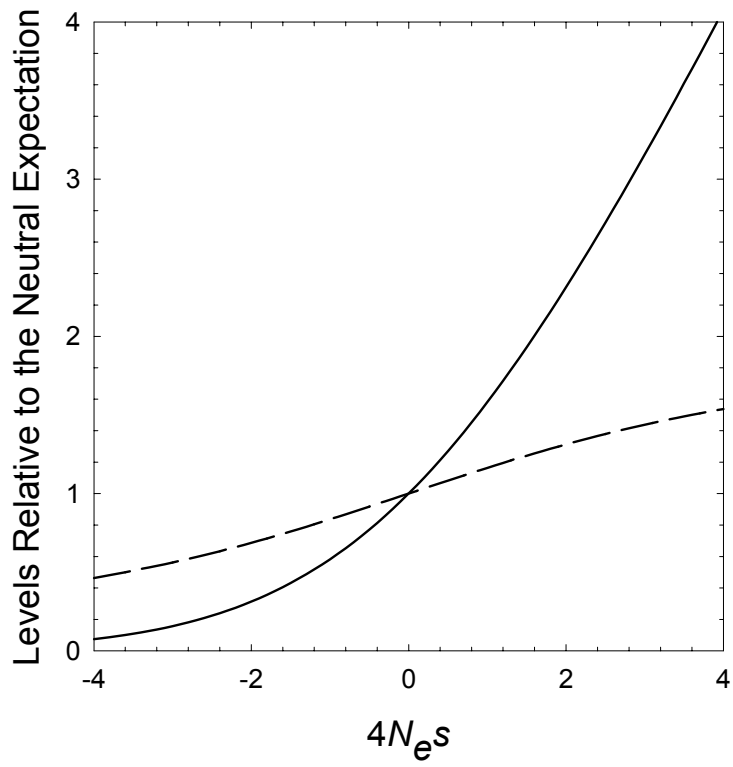
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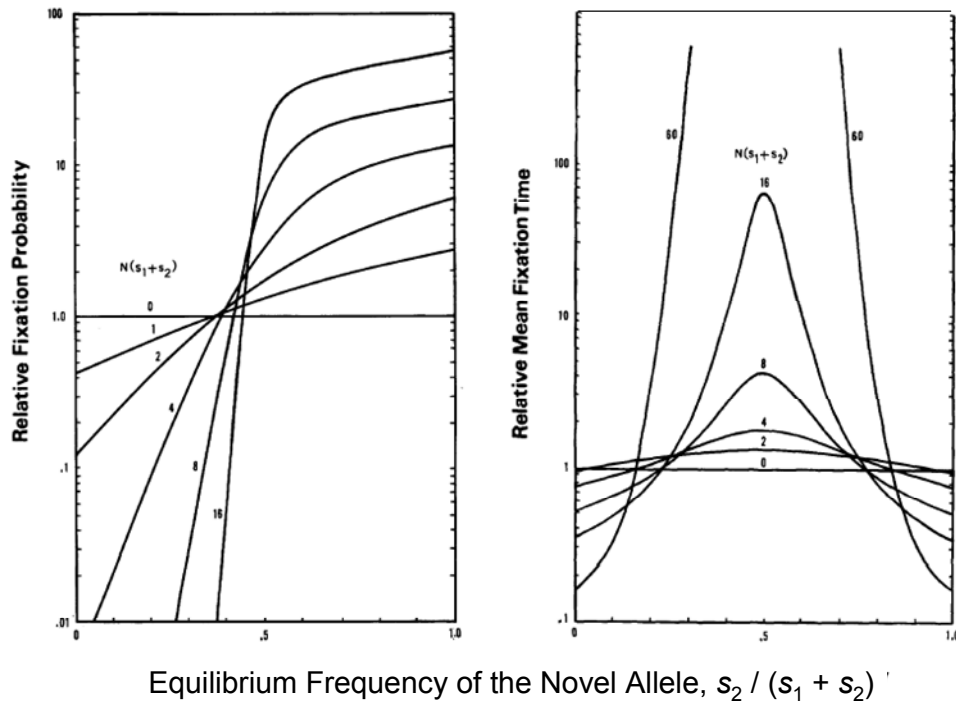
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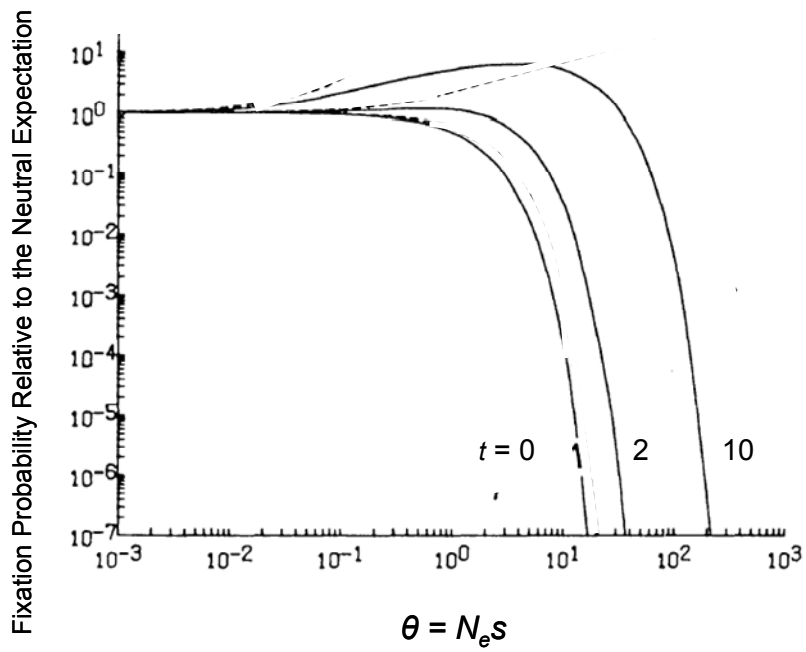
**Figure 8.1.** Probability of fixation and lifetime contribution to heterozygosity of a new mutant allele with additive effects on fitness as a function of  $N_e s$  (using Equations 8.12a and 8.13), both relative to the neutral expectation.



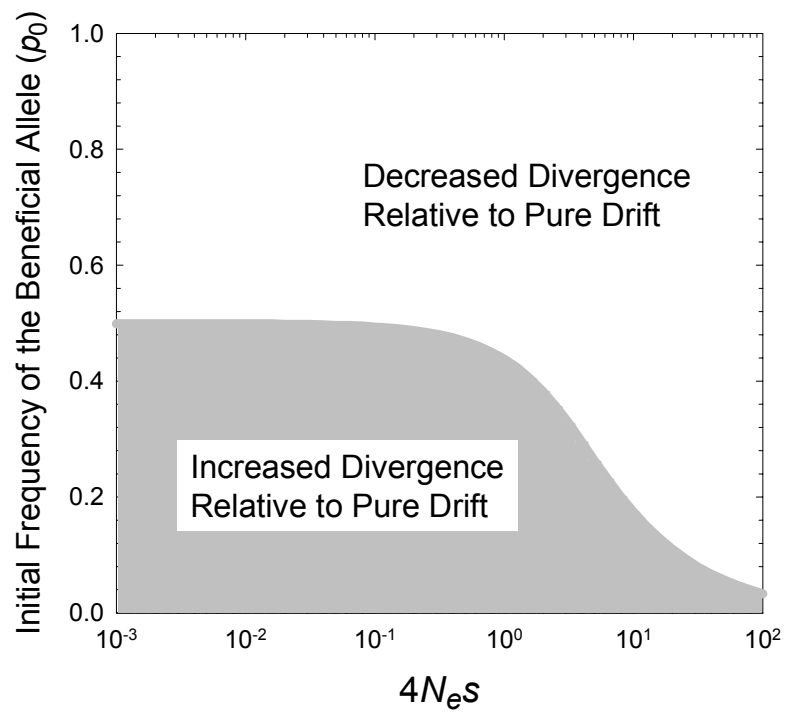
**Figure 8.2.** Ratios for the fixation probabilities and expected times to fixation for a newly arisen overdominant mutation relative to the expectations for neutral mutations, as a function of the equilibrium frequency expected in a population of infinite size  $\tilde{p} = s_2 / (s_1 + s_2)$ , where the fitnesses are  $1 - s_1$ , 1, and  $1 - s_2$  (the former being for the mutant homozygote). Each curve gives results for a different value of  $N_e(s_1 + s_2)$ , a measure of the ratio of the power of selection to drift, where  $N_e$  is the effective population size. For any value of  $N_e(s_1 + s_2)$ , the probability of fixation increases with the magnitude of selection against the alternative homozygote, as this defines the selective advantage of the novel allele in the heterozygous state. From Nei and Roychoudhury (1973).



**Figure 8.3.** The probability of fixation of a newly arisen underdominant mutation, relative to the neutral expectation of  $1/(2N)$ , with selective disadvantage  $s$  in the heterozygous state and advantage  $t$  in the homozygous state. From Walsh (1982).



**Figure 8.4.** The Cohan effect. A diallelic locus under additive selection is considered. The shaded area is the region of  $p_0$  (the initial frequency of **A**) and  $4N_e s$  space where the probability that isolated populations are fixed for alternative alleles is higher under selection and drift than under drift alone. In this region, selection increases the amount of indeterminism relative to drift alone.



**Figure 8.5.** The decline in the mean time between peak shifts in a system involving compensatory mutations, where the endpoints are selectively equivalent and the intermediate states have selective disadvantage  $s$ . The results are obtained by solving Equations 8.43 and 8.44 with mutation rate  $u = 10^{-8}$ .

